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# Quantification of Coronary Atherosclerosis and Inflammation to Predict Coronary Events and All-Cause Mortality

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**Objectives** This study sought to determine whether the evaluation of the combined presence of coronary artery calcium (CAC) and high-sensitivity C-reactive protein (hsCRP) improves discrimination and stratification of hard coronary events and all-cause mortality in the general population.

**Background** Coronary atherosclerosis is a chronic inflammatory disease. Both hsCRP as a measure of inflammation and CAC as a measure of coronary plaque burden have been shown to improve risk appraisal.

**Methods** Framingham risk variables, hsCRP, and CAC were measured in 3,966 subjects without known coronary artery disease or acute inflammation. After 5 years, incident coronary deaths, nonfatal myocardial infarction, and all-cause mortality were determined.

**Results** CAC and hsCRP independently predicted 91 coronary events (adjusted hazard ratios [HRs]: $\log_2(CAC+1) = 1.25$ [95% confidence interval (CI): 1.16 to 1.34], $p < 0.0001$; hsCRP = 1.11 [95% CI: 1.02 to 1.21], $p = 0.019$) and 130 deaths (adjusted HRs: $\log_2(CAC+1) = 1.12$ [95% CI: 1.06 to 1.19], $p < 0.0001$; hsCRP = 1.11 [95% CI: 1.04 to 1.19], $p = 0.004$). For coronary events, net reclassification improvement (NRI) was 23.8% ($p = 0.0007$) for CAC and 10.5% ($p = 0.026$) for hsCRP. Adding CAC to Framingham risk variables and hsCRP further improved discrimination of coronary risk but not vice versa. Among persons without CAC, those with hsCRP >3 mg/l versus <3 mg/l had a significantly higher coronary risk ($p = 0.006$). For all-cause mortality, integrated discrimination improvement (IDI) was positive when CAC or hsCRP were added to age and sex (+0.51%, $p < 0.001$ and +0.43%, $p = 0.012$, respectively). Adjusted HRs in the highest versus lowest category of a risk index derived from established CAC and hsCRP thresholds (i.e., CAC = 100 and hsCRP = 3 mg/l) were 5.92 (95% CI: 3.14 to 11.16) for coronary events and 3.02 (95% CI: 1.82 to 5.01) for all-cause mortality ($p < 0.0001$ each). The adjusted HR for coronary events in intermediate risk subjects was 6.98 (95% CI: 2.47 to 19.73), $p < 0.001$.

**Conclusions** The risk of coronary events and all-cause mortality that is mediated by the presence of coronary atherosclerosis and systemic inflammation can be estimated by CAC and hsCRP. An improvement in coronary risk prediction and discrimination was predominantly driven by CAC, whereas hsCRP appears to have a role especially in persons with very low CAC scores. (J Am Coll Cardiol 2011;57:1455–64) © 2011 by the American College of Cardiology Foundation

Atherosclerosis is a chronic inflammatory disease responsible for the majority of coronary events and deaths in the Western world (1,2). Traditional coronary risk stratification algorithms have well-known limitations for individual risk assessment. High-sensitivity C-reactive protein (hsCRP) as a measure of inflammation and coronary artery calcium

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**Abbreviations and Acronyms**

AUC = area under the curve
BMI = body mass index
CAC = coronary artery calcium
CI = confidence interval
CVD = cardiovascular disease
EBCT = electron-beam computed tomography
FRS = Framingham risk score
HDL = high-density lipoprotein
HR = hazard ratio
hsCRP = high-sensitivity C-reactive protein
IDI = incremental discrimination improvement
LDL = low-density lipoprotein
NRI = net reclassification improvement

(CAC) as a measure of coronary plaque burden have both been shown to improve risk appraisal in individuals (3–7).

High-sensitivity CRP is a systemic marker of inflammation and has been found in many (8–10), but not all (11,12), studies to be an independent predictor of cardiovascular events and of all-cause mortality (13). It has also been suggested to be useful in guiding treatment decisions (14). However, the predictive value of CRP for risk stratification when added to the Framingham risk score remains controversial (10,15–17).

Coronary artery calcium is an estimate of overall coronary artery plaque burden and an independent predictor of coronary events and of all-cause mortality (3–5,18–20). Yet, little is known about whether and how hsCRP modifies the predictive value of CAC and vice versa. The correlation between CAC and CRP is weak and largely determined by the presence of risk factors (21), which suggests an independent role of atherosclerosis burden and inflammation in event manifestation. Yet, few studies have thus far assessed the predictive value of the combined presence of elevated CAC and CRP for coronary events. These studies yielded conflicting results (22,23), and their combined role for predicting all-cause mortality has not been studied.

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The Heinz Nixdorf Recall (HNR) study is a population-based cohort study designed to assess the predictive value of novel markers of risk when used in addition to traditional risk factors (3,24). The aim of this study was to determine the value of hsCRP and CAC and their combination in extended coronary event and all-cause mortality risk appraisal.

## Methods

**Participants.** Participants were randomly selected from mandatory city registries in Essen, Bochum, and Mülheim, and invited to participate in the study as previously reported (3,24). Physician- or self-referral was not allowed to avoid selection bias. A total of 4,814 subjects aged 45 to 75 years (50% females) were included between December 2000 and August 2003. All subjects with physician-diagnosed coronary artery disease, that is, a history of myocardial infarction or coronary revascularization (n = 327) were excluded from the study. Of the remaining participants, n = 34 (0.8%) were lost to follow-up, in n = 94 (2.1%), we were unable to obtain 5-year primary end point information, and in n = 244 (5.4%), 1 or more measurements of cardiovascular risk factors, hsCRP, or CAC were unavailable. Subjects with hsCRP >10 mg/l suggesting acute inflammation were excluded (n = 149, 3.3%), leaving 3,966 subjects (53% women) for this analysis. All participants provided written informed consent, and the study was approved by the ethical committee at the University Essen, Germany.

**Cardiovascular risk factors and questionnaires.** Blood pressure was determined from the mean value of the second and third of 3 measurements taken at least 3 min apart (Omron 705-CP, OMRON, Mannheim, Germany) and classified according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) threshold values (25). Body mass index (BMI) was calculated from standardized measurements of height and weight. Current smoking was defined as a history of cigarette smoking during the past year. Standard enzymatic methods were used to measure total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglycerides. Participants were considered diabetic if they reported a physician diagnosis of diabetes or were taking antidiabetic medication. From these risk factors, the Framingham risk score (FRS) (i.e., predicted 10-year risk) was computed (26). High-sensitivity CRP was measured using a standardized assay (Roche Diagnostics, Basel, Switzerland).

All subjects were queried about known cardiovascular disease (CVD) using a physician-based questionnaire and about regular cardiovascular medication including antihypertensive medication, lipid-lowering drugs, platelet aggregation inhibitors, or glycosides.

**Electron-beam computed tomography (EBCT).** To quantify CAC, nonenhanced EBCT scans were performed with a C-150 scanner (GE Imatron, South San Francisco, California). Prospective electrocardiogram triggering was done at 80% of the RR interval. Contiguous 3-mm-thick slices to the apex of the heart were obtained in both studies at an image acquisition time of 100 ms. Coronary artery calcium was defined as a focus of at least 4 contiguous pixels with a CT density ≥130 Hounsfield units. The CAC Agatston score was computed by summing the CAC scores of all foci in the epicardial coronary system (27). Neither the CAC score nor hsCRP values were communicated to either the participants or their treating physicians.

**A combined risk index based on hsCRP and CAC.** An index for the combined assessment of atherosclerosis burden and inflammation was defined based on previously defined and clinically used thresholds (28), that is, CAC = 100 and a hsCRP = 3.0 mg/l, resulting in 4 possible combinations: 1) hsCRP ≤3 mg/l and CAC <100; 2) hsCRP >3 mg/l and CAC <100; 3) hsCRP ≤3 mg/l and CAC ≥100; and 4) hsCRP >3 mg/l and CAC ≥100.

**Follow-up.** Annual postal questionnaires assessed the morbidity status during follow-up, that is medication, hospital admissions, outpatient diagnoses of CVD. Self-reported incident cardiovascular morbidity and of fatal events was validated by review of hospital records and records of the attending physicians (see the following text). All death certificates of the 3 cities under study were regularly screened. In parallel, deceased participants were tracked back to obtain as much information as possible to verify causes of death.

Participants were followed for a median of 5.0 years (5.1 ± 0.3 years). The vital status could be obtained from 99.2% of subjects and information on primary end points from 97.1% of subjects.

**Study end points and verification of study end points.** Primary end points for this study were based on unequivocally documented incident coronary events that met predefined study criteria (3,24). We considered a myocardial infarction event based on symptoms, electrocardiographic signs, and enzymes (levels of creatine kinase [CK-MB]) as well as troponin T or I, and necropsy as: 1) nonfatal acute myocardial infarction; and 2) coronary death, which occurred between the baseline examination and 5 years after study entry (29).

For all primary study end points, hospital and nursing home records including electrocardiograms, laboratory values, and pathology reports were collected. For deceased subjects, death certificates were collected, and interviews with general practitioners, relatives, and eyewitnesses were undertaken where possible. Medical records were obtained for all reported end points. An external criteria and end point committee blinded for conventional risk factor status and CAC scores reviewed all documents and classified the end points thereafter.

**Statistical analysis.** Demographic data and risk factors are expressed as mean ± SD or median (25th, 75th percentile), frequencies are given as counts (%). Differences in proportions were statistically evaluated using chi-square or Fisher exact test, trends in proportions using the Cochran-Armitage trend test; location measures of continuous quantities were compared using Student *t* test or Mann-Whitney *U* statistics.

The FRS categories were <10%, 10% to 20%, and >20% of 10-year predicted coronary heart disease risk. Observed 5-year cumulative risks are given in FRS and predefined CAC score categories 0, 1 to 99, 100 to 399, and ≥400 as well as FRS and hsCRP categories <1, 1 to 3, and >3 mg/l (24,27). Cumulative coronary event risks are also calculated stratified by the FRS and the combined risk index. Kaplan-Meier estimates of coronary event-free rates as well as overall survival were calculated in strata defined by the combined risk index. We used multivariable Cox proportional hazard regression to calculate unadjusted and adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) with respect to CAC categories, hsCRP categories, or the combined risk index, for the time to occurrence of end points. Adjustment accounted for FRS, presence of any cardiovascular disease or cardiovascular medication, for BMI, and also for hsCRP for the model with CAC, or for the logarithmic transform of CAC, log(CAC+1), for the model with hsCRP. Schoenfeld residuals were calculated to evaluate the validity of the proportional hazards assumption (30). To estimate the increase in prediction accuracy, we used logistic regression to calculate the receiver-operator characteristic curves and the area under the receiver-operator characteristic curves (AUC or c-statistic) including 95% confidence intervals and compared the AuC based on the FRS alone, the AuC when adding the log-transformed CAC score or hsCRP, and finally, when adding log-(CAC+1) and hsCRP to the FRS (31). This was also carried out for a model with Framingham risk variables (age, sex, diabetes, systolic blood pressure, LDL and HDL cholesterol, present smoking status) with and without log(CAC+1) and/or hsCRP. The latter models also served to estimate the integrated discrimination improvement (IDI) (32). The same route was followed for all-cause mortality, but with the model consisting of age and sex as the starting point. Net reclassification improvement (NRI) was computed for coronary events (32), but not for all-cause mortality as no predefined thresholds for low, intermediate, or high risk have been published. Rescaled individual predicted risks from models with and without log(CAC+1) and/or hsCRP were compared with established Framingham risk thresholds. The rescaling factor was derived by dividing the average 10-year Framingham risk, that is, 11.29%, by the observed 5-year event rate, that is, 2.29%, yielding a rescaling factor of 4.92. In addition to the AUCs, we computed Harrell's c-statistics for time-to-event data (33). To evaluate model calibration, we calculated the Hosmer-Lemeshow chi-square. All calculations were performed with SAS version 9.2 (Cary, North Carolina).

## Results

**Incidence of coronary events and all-cause mortality.** After 5.1. ± 0.3 years of follow-up, 91 subjects experienced coronary events. Twenty-nine subjects (31% women) died of coronary heart disease, and 62 subjects (29% women) had a nonfatal myocardial infarction. Of those with nonfatal myocardial infarction as their first event, 4 died later, 3 of coronary causes. In addition, 98 noncoronary deaths occurred (main cause: 54 cancer-related deaths). Table 1 shows characteristics of subjects with and without coronary events. Deceased persons also had higher Framingham risk scores (median [Q1/Q3]: 14 [9/22] vs. 9 [6/14], $p < 0.0001$), higher CAC scores (73 [9/372] vs. 11 [0/106], $p < 0.0001$), and higher hsCRP values (2.2 [1.1/4.4] vs. 1.4 [0.7/2.8], $p < 0.0001$).

**Table 1** Distribution of Risk Variables in Subjects With Versus Those Without Coronary Events During 5 Years of Follow-Up

| | No Coronary Events | Coronary Events | p Value |
|---|---|---|---|
| n | 3,875 | 91 | |
| Age, yrs | 59.2 ± 7.7 | 62.8 ± 8.2 | <0.0001 |
| Female | 53.4 | 29.7 | <0.0001 |
| BMI | 27.7 ± 4.5 | 28.2 ± 4.4 | 0.29 |
| Systolic BP, mm Hg | 133 ± 21 | 143 ± 23 | <0.0001 |
| Diastolic BP, mm Hg | 81 ± 11 | 83 ± 12 | 0.082 |
| Hypertension | 53.9 | 67.0 | 0.013 |
| Total cholesterol, mg/dl | 231 ± 39 | 238 ± 38 | 0.10 |
| LDL cholesterol, mg/dl | 146 ± 36 | 155 ± 35 | 0.019 |
| HDL cholesterol, mg/dl | 59 ± 17 | 54 ± 17 | 0.006 |
| Smoking status | | | |
| Never | 44.2 | 36.2 | |
| Current | 22.5 | 27.5 | 0.29 |
| Former | 33.3 | 36.3 | |
| Diabetic | 7.0 | 17.6 | 0.0001 |
| CV medication* | 35.3 | 51.7 | 0.0013 |
| Lipid-lowering drugs | 9.1 | 11.0 | 0.54 |
| Antihypertensive medication | 31.3 | 47.3 | <0.001 |
| Cardiovascular diseases | 23.6 | 23.1 | 0.90 |
| FRS | | | |
| 10-yr FRS | 11.1 ± 8.2 | 17.6 ± 11.4 | <0.0001 |
| Median (Q1–Q3) | 9 (6–14) | 14 (9–24) | |
| <10% in 10 yrs | 55.2 | 27.5 | |
| 10–20% in 10 yrs | 32.7 | 40.7 | <0.0001 |
| >20% in 10 yrs | 12.1 | 31.9 | |
| CAC score | | | |
| Median (Q1–Q3) | 11 (0–105) | 182 (31–982) | <0.0001 |
| 0 | 32.9 | 12.1 | |
| >0–99 | 41.3 | 26.4 | |
| 100–399 | 16.4 | 25.3 | <0.0001 |
| ≥400 | 9.4 | 36.3 | |
| hsCRP, mg/l | | | |
| Median (Q1–Q3) | 1.4 (0.7–2.9) | 2.1 (0.9–4.8) | 0.0007 |
| <1 | 35.2 | 25.3 | |
| 1–3 | 42.6 | 34.1 | 0.0003 |
| >3 | 22.2 | 40.7 | |
| Combined risk index | | | |
| I: hsCRP ≤3, CAC <100 | 58.8 | 24.2 | |
| II: hsCRP >3, CAC <100 | 15.4 | 14.3 | <0.0001 |
| III: hsCRP ≤3, CAC ≥100 | 19.0 | 35.2 | |
| IV: hsCRP >3, CAC ≥100 | 6.8 | 26.4 | |

Values are mean ± SD or % unless otherwise indicated. *CV medication includes blood pressure lowering or lipid-lowering medication.
BMI = body mass index; BP = blood pressure; CAC = coronary artery calcium; Chol = cholesterol; CV = cardiovascular; FRS = Framingham risk score; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; Hx = history; LDL = low-density lipoprotein; Q = quartile.

**Prediction of coronary events and all-cause mortality using CAC or hsCRP.** Crude and adjusted HRs of coronary events and of all-cause mortality increased with increasing CAC and hsCRP categories (Table 2) and reached statistical significance with CAC ≥100 or hsCRP >3 mg/l for coronary events and with CAC >0 or hsCRP ≥1 mg/l for all-cause mortality. Adjusted HRs of all-cause mortality (as in Table 2, Model 2) were not much different when coronary deaths were excluded (data not shown).

In multivariable Cox regression models including known CVD, cardiovascular medication, the FRS, BMI, CAC, and hsCRP, both CAC and hsCRP remained predictors of coronary events: HR: 1.25 (95% CI: 1.16 to 1.34), $p < 0.0001$ for $\log_2(CAC+1)$ and HR: 1.11 (95% CI: 1.02 to 1.21), $p = 0.019$ for hsCRP. CAC and hsCRP were also independent predictors of all-cause mortality (HR: 1.12 [95% CI: 1.06 to 1.19], $p < 0.0001$ for $\log_2(CAC+1)$ and HR: 1.11 [95% CI: 1.04 to 1.19], $p = 0.004$ for hsCRP). These estimates did not change much when coronary deaths were excluded (data not shown). In a model including $\log_2(CAC+1)$, hsCRP, and their product, we found no interaction between CAC and hsCRP for coronary events

**Table 2** Crude and Adjusted HR (95% CI) of Coronary Events and All-Cause Mortality in the CAC and hsCRP Categories

| | Coronary Events | | | All-Cause Mortality | | |
|---|---|---|---|---|---|---|
| | Crude HR (95% CI) | Adjusted HR (95% CI) Model 1 | Adjusted HR (95% CI) Model 2 | Crude HR (95% CI) | Adjusted HR (95% CI) Model 1 | Adjusted HR (95% CI) Model 2 |
| CAC score | | | | | | |
| 0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| >0–99 | 1.75 (0.86–3.58) | 1.47 (0.71–3.05) | 1.48 (0.72–3.07) | 2.94 (1.66–5.20) | 2.44 (1.36–4.37) | 2.45 (1.37–4.38) |
| 100–399 | 4.19 (2.04–8.59) | 3.01 (1.43–6.33) | 3.03 (1.44–6.38) | 4.10 (2.21–7.59) | 2.82 (1.49–5.36) | 2.82 (1.48–5.36) |
| ≥400 | 10.37 (5.24–20.52) | 6.00 (2.86–12.59) | 5.92 (2.82–12.45) | 6.54 (3.51–12.21) | 3.79 (1.94–7.42) | 3.71 (1.89–7.28) |
| hsCRP, ml/l | | | | | | |
| <1 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| 1–3 | 1.19 (0.65–1.92) | 0.95 (0.55–1.65) | 0.95 (0.55–1.64) | 1.87 (1.16–2.99) | 1.71 (1.05–2.79) | 1.72 (1.06–2.79) |
| >3 | 2.56 (1.52–4.31) | 1.98 (1.14–3.43) | 1.82 (1.05–3.15) | 3.10 (1.91–5.01) | 2.63 (1.57–4.38) | 2.53 (1.52–4.23) |

Model 1: adjusted for FRS, known CV disease or CV medication and BMI. Model 2: adjusted for FRS, known CV disease or CV medication, BMI, and hsCRP or CAC.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

(HR: 0.99 [95% CI: 0.96 to 1.01], p = 0.26) or for all-cause mortality (HR: 1.00 [95% CI: 0.98 to 1.02], p = 0.66). In none of these models was a deviation from the proportional hazards assumption detected.

**Measures of discrimination (c-statistics, IDI, NRI).** Upon adding CAC to the model based on Framingham risk factors for coronary event risk assessment, AUCs, IDI, and NRI indicated improvement, whereas when adding hsCRP, only NRI, but not AUCs and IDI, showed discrimination improvement (Table 3). Calibration (Hosmer-Lemeshow) yielded a chi-square of 11.5 (p = 0.18) for the model with Framingham risk variables. This value decreased to 7.1 (p = 0.53) when log(CAC+1) and hsCRP were entered into the model. Adding CAC to the model based on Framingham risk factors and hsCRP further improved discrimination as indicated by AUCs, IDI, and NRI, whereas adding hsCRP to the model based on Framingham risk factors and CAC did not (Table 3).

Adding CAC to the model based on age and sex or to the model based on age, sex, and hsCRP to predict all-cause mortality resulted in positive IDIs, whereas improvements in the AUCs were marginal (Table 3). Adding hsCRP to the model based on age and sex significantly increased AUC with IDI being positive. Also, hsCRP further increased AUC with IDI being positive when added to the model based on age, sex, and CAC (Table 3). For all-cause mortality, calibration yielded a chi-square of 12.9 (p = 0.11) for the model with age and sex. This value decreased to 7.1 (p = 0.52) when log(CAC+1) and hsCRP were entered into the model.

The c-statistics from time-to-event analyses (Harrell's c), as well as IDI and NRI from time-to-event analysis, were numerically almost identical to c-statistics, IDI, and NRI from logistic regression for both end points (data not shown).

**Coronary risk and all-cause mortality stratified by CAC and hsCRP categories and a risk index derived from CAC and hsCRP categories.** In each hsCRP category, adjusted HRs of coronary events and of all-cause mortality generally increased with each CAC category and vice versa

**Table 3** c-Statistics, IDI, and NRI for the Combined Assessment of Traditional Markers of Risk, hsCRP, and log(CAC+1) in Predicting Coronary Events and All-Cause Mortality

| | | Coronary Events Model Based on Framingham Risk Variables* | | | All-Cause Mortality Model Based on Age and Sex | |
|---|---|---|---|---|---|---|
| Model No. | Model | c-Statistics | IDI | NRI | c-Statistics | IDI |
| 1. | Base model alone | 0.719 (0.671–0.767) | / | / | 0.695 (0.647–0.743) | / |
| 2. | 1. + hsCRP | 0.732 (0.684–0.780) | 0.0015 | 10.5% | 0.712 (0.666–0.758) | 0.0043 |
| | p value vs. model 1 | 0.12 | 0.32 | 0.026 | 0.044 | 0.012 |
| 3. | 1. + log(CAC+1) | 0.763 (0.715–0.812) | 0.0148 | 23.8% | 0.706 (0.660–0.752) | 0.0051 |
| | p value vs. model 1 | 0.0067 | <0.0001 | 0.0007 | 0.21 | 0.0006 |
| 4. | 1. + hsCRP and log(CAC+1) | 0.771 (0.724–0.819) | 0.161 vs. model 1 | 20.5% vs. model 1 | 0.719 (0.675–0.763) | 0.0090 vs. model 1 |
| | | | 0.146 vs. model 2 | 13.3% vs. model 2 | | 0.0047 vs. model 2 |
| | | | 0.013 vs. model 3 | −2.2% vs. model 3 | | 0.0039 vs. model 3 |
| | p value vs. model 1 | 0.0014 | 0.0001 | 0.0027 | 0.025 | 0.0003 |
| | p value vs. model 2 | 0.014 | <0.0001 | 0.031 | 0.33 | 0.0014 |
| | p value vs. model 3 | 0.12 | 0.44 | 0.50 | 0.067 | 0.023 |

Net reclassification improvement (NRI) was computed for coronary events only, because of the lack of established thresholds of risk for all-cause mortality. Note that the NRI for hsCRP was 6.8% (p = 0.053) and for CAC was 19.8% (p = 0.003) when lower and upper intermediate risk thresholds were defined as 6% and 20% in 10 years. / indicates not applicable. *Including age, sex, diabetes, systolic blood pressure, LDL and HDL cholesterol, and present smoking status.
IDI = incremental discrimination improvement; other abbreviations as in Table 1.

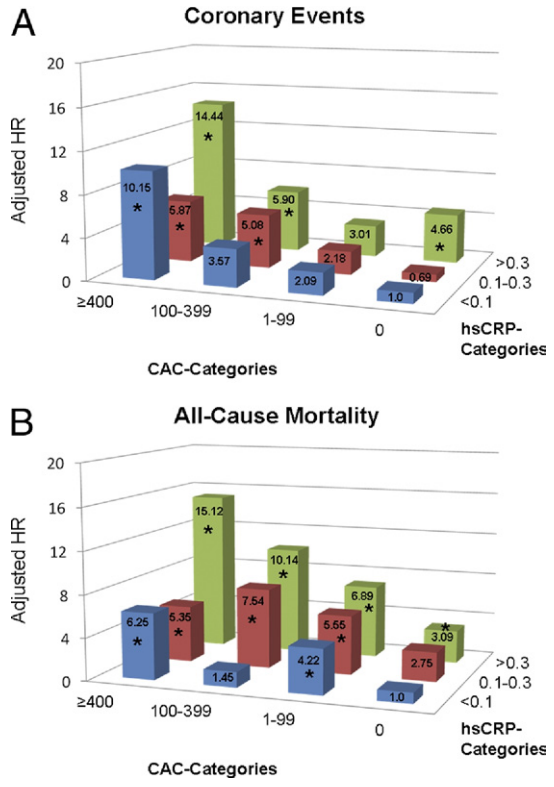


**Figure 1** **Adjusted HRs of Coronary Events and of All-Cause Mortality in the Different Combinations of CAC and hsCRP Categories**

**(A)** Coronary events and **(B)** all-cause mortality, with coronary artery calcium (CAC) = 0 and high-sensitivity C-reactive protein (hsCRP) <1 mg/l as the reference category. Hazard ratios (HRs) were adjusted for the Framingham risk score, known cardiovascular disease, cardiovascular medication, and body mass index. *Significant difference from the reference category.

(Fig. 1). Cumulative risks of coronary events and of all-cause mortality increased with increasing CAC scores within each hsCRP category (cumulative risks not shown, $p < 0.0001$ for trend each). In the lowest and in the highest CAC categories, the cumulative risk was higher for those with hsCRP >3 mg/l versus hsCRP ≤3 mg/l ($p = 0.006$ and $p = 0.017$, respectively). The increase in cumulative all-cause mortality risk observed for increasing hsCRP categories was significant within the 2 highest CAC categories ($p = 0.007$ and $p = 0.007$ for trend, respectively).

Coronary event-free rates and overall survival decreased with increasing CAC, hsCRP, and risk index categories (Fig. 2). When coronary deaths were excluded from analysis of all-cause mortality, adjusted HRs for the risk index did not change much, that is, to 1.0, 1.37 (95% CI: 0.76 to 2.45), 0.91 (95% CI: 0.51 to 1.62), and 2.67 (95% CI: 1.51 to 4.74).

The comparison of c-statistics and IDI for the risk index compared with CAC categories did not show any statistically significant differences either for coronary event risk or for all-cause mortality risk ($p > 0.1$ each).

**Coronary risk in different Framingham risk score categories.** Within each Framingham risk category, the cumulative coronary event risk increased with increasing CAC, hsCRP, and risk index categories (Figs. 3A to 3C). Of note, in each Framingham risk category, event rates were similarly low when CAC was <100 and hsCRP <3 mg/l (Fig. 3C). In intermediate-risk subjects, coronary event-free rates were similar when intermediate risk was defined as a risk between 6% and 20% in 10 years (Figs. 4A to 4C).

## Discussion

This study shows that the risk of coronary events and all-cause mortality that is mediated by the presence of coronary atherosclerosis and systemic inflammation can be estimated by measuring CAC and hsCRP, and that their combined assessment can be used for improved risk stratification and discrimination in the general population. Adding CAC or hsCRP to traditional risk factors improved coronary and all-cause mortality risk stratification in a magnitude comparable to previous prospective studies (3,4,6). The ability of CAC to improve discrimination and net reclassification of coronary risk was superior to that of hsCRP, and CAC further improved measures of coronary risk discrimination when added to Framingham risk variables and hsCRP, whereas adding hsCRP to Framingham risk variables and CAC did not. Yet, in subjects without CAC, hsCRP was associated with a relevant increase in coronary risk. Both CAC and hsCRP were of similar and additive value for improved discrimination of all-cause mortality. A simple, previously suggested risk index (28) derived from established CAC and hsCRP thresholds also identified many persons at clearly elevated or low risk, but it did not improve overall discrimination beyond CAC scoring.

Three studies directly compared the predictive values of CRP (but not hsCRP) and CAC. First, 967 nondiabetic subjects, mostly men with an average age of 66 years, who experienced coronary events during 6.4 years follow-up had much higher CAC scores ($p < 0.0001$) and higher CRP values ($p = 0.007$) than those without, but the independent effect of CRP was of borderline significance (23). Second, in 4,903 asymptomatic persons of the St. Francis Heart Study age 50 to 70 years, CRP did not contribute to coronary event prediction after adjustment for standard risk factors and the baseline CAC score (22). Third, in a preliminary report from the MESA (Multi-Ethnic Study of Atherosclerosis) (34), fully adjusted HRs for CVD events were 1.41 (95% CI: 0.98 to 2.04) for CRP >3 mg/l compared with <1 mg/l. Interestingly, as in our study, the coronary event risk was much higher in subjects with low CAC scores and high versus low CRP values (34). In contrast to our study, the

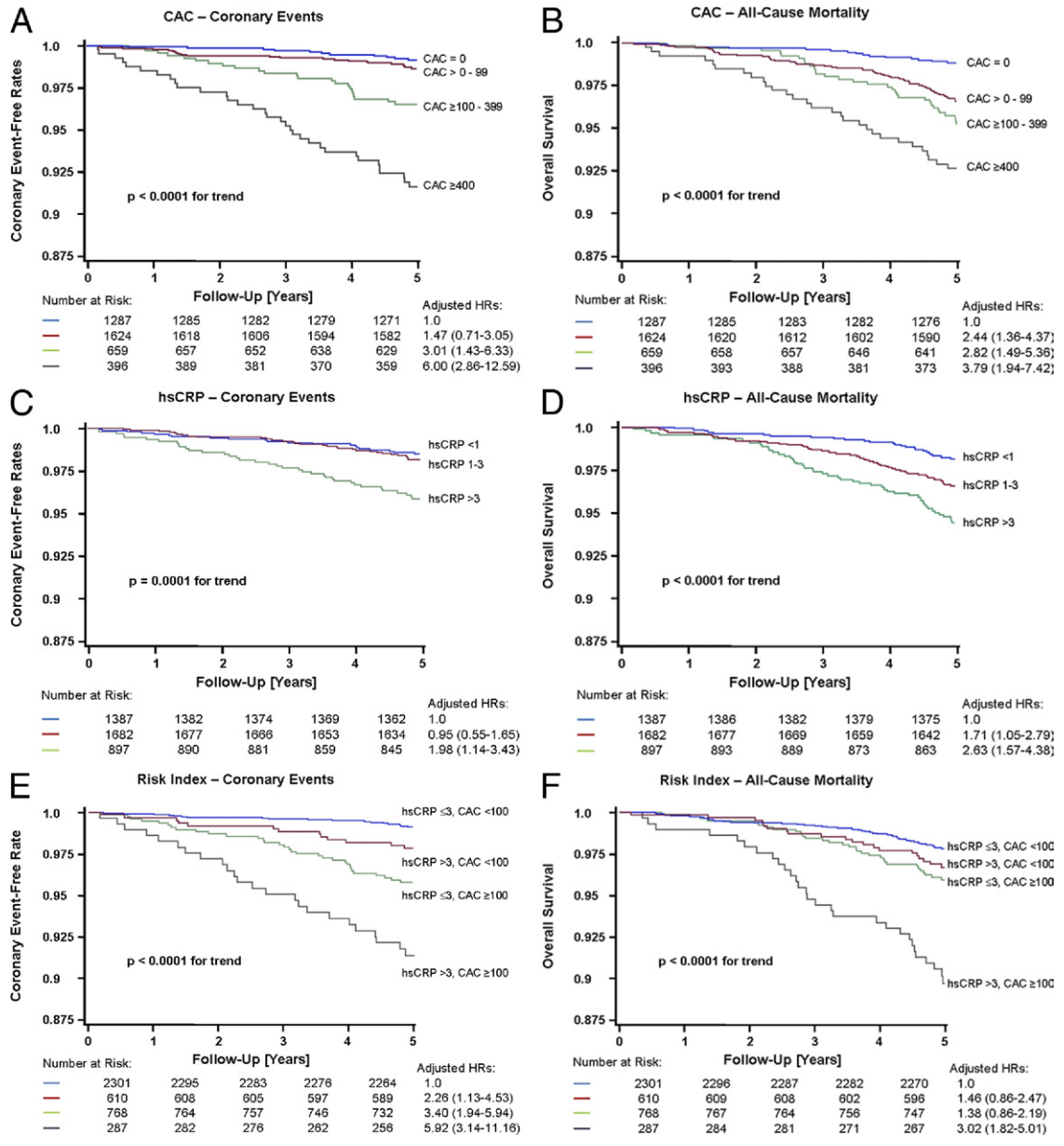


**Figure 2** **Coronary Event-Free Rates and Overall Survival Stratified by CAC, hsCRP, and a Risk Index Derived From CAC and hsCRP**

**(A, C, E)** shows the coronary event-free rates and **(B, D, F)**, overall survival. HRs were adjusted for the Framingham risk score, known cardiovascular disease, cardiovascular medication, and body mass index. Abbreviations as in Figure 1.

latter 2 studies used broader coronary event definitions, CRP but not hsCRP was measured, and none of these 3 studies have evaluated the joint effect of CAC and CRP on all-cause mortality.

There is an ongoing debate on the value of including markers of atherosclerosis and inflammation into traditional risk assessment (17,21,35). A combined approach appears promising as coronary plaque burden and systemic inflammation seem to have distinct roles in the pathogenesis of different events. Although CAC is a surrogate of overall coronary atherosclerosis burden, but not necessarily of vulnerable plaque, systemic inflammation may predispose to a higher likelihood of plaque rupture and thrombosis (21). As coronary events predominantly occur in the presence of extensive coronary plaque burden (36), a high CAC score had a particularly strong impact in predicting coronary events. hsCRP contributed to risk assessment in subjects with little or no coronary atherosclerosis, where fewer events occurred.

All-cause mortality is only in part determined by CVD events, and the predictive value of CAC was accordingly lower

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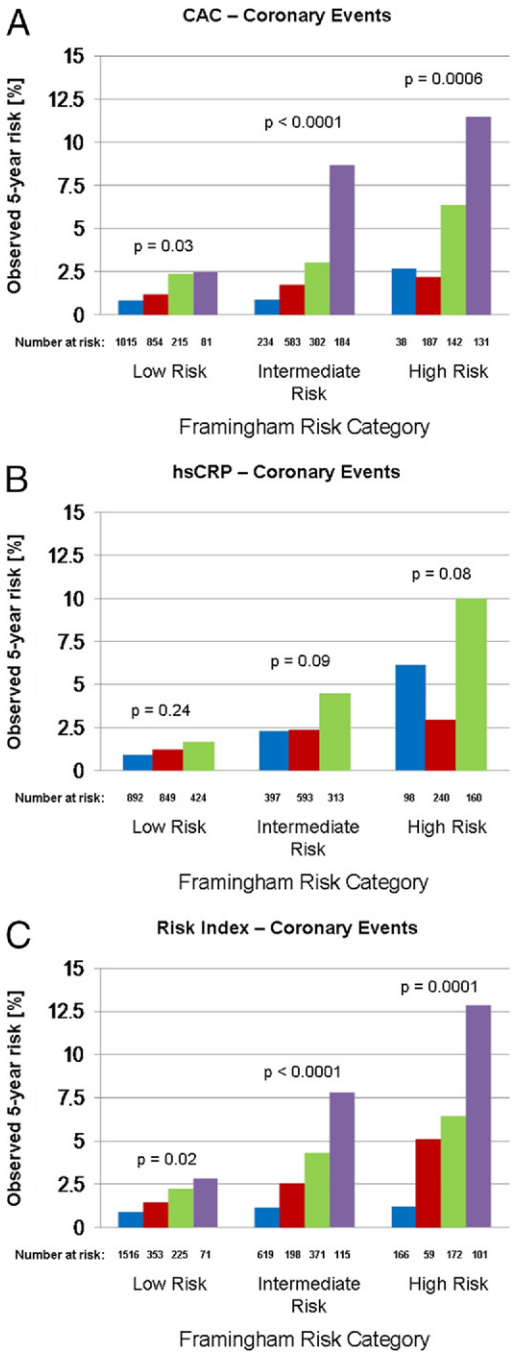


**Figure 3** Cumulative Observed 5-Year Coronary Event Risks Within FRS Categories Stratified by CAC, hsCRP, and the Risk Index

**(A)** CAC, **(B)** hsCRP, and **(C)** the risk index. Within the intermediate Framingham risk score (FRS) category, defined as 10% to 20% risk in 10 years, HRs in the second, third, and fourth compared with the first risk category were for CAC: 2.14 (95% confidence interval [CI]: 0.47 to 9.82), 2.68 (95% CI: 0.79 to 17.09), and 10.34 (95% CI: 2.34 to 45.66); for hsCRP: 1.09 (95% CI: 0.47 to 2.54) and 2.01 (95% CI: 0.84 to 4.82); and for the risk index: 2.38 (95% CI: 0.75 to 7.57), 3.84 (95% CI: 1.58 to 9.36), and 6.98 (95% CI: 2.47 to 19.73), respectively. p values for trend within FRS categories. Note that the cumulative 5-year event rates were very similar in all 3 FRS categories when both CAC and hsCRP were low, that is, 0.9% (95% CI: 0.5% to 1.5%), 1.1% (95% CI: 0.5% to 2.3%), and 1.2% (95% CI: 0.2% to 4.3%), respectively. Abbreviations as in Figure 1.

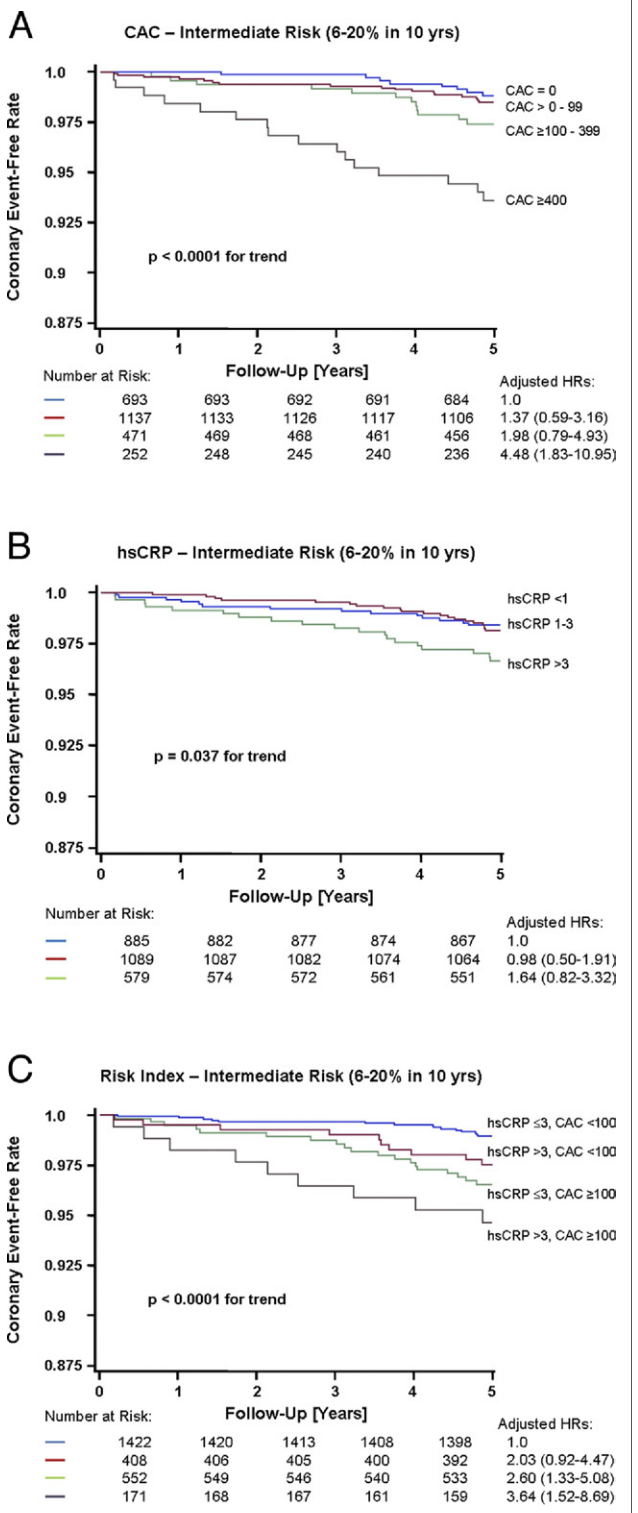


**Figure 4** Coronary Event-Free Rates in Intermediate-Risk Subjects Stratified by CAC, hsCRP, and the Risk Index Derived From CAC and hsCRP

**(A)** CAC, **(B)** hsCRP, and **(C)** the risk index. Intermediate risk is defined as 6% to 20% predicted coronary event risk in 10 years. HRs were adjusted for the Framingham risk score, known cardiovascular disease, cardiovascular medication, and body mass index. Abbreviations as in Figure 1.

compared with its value in predicting coronary events. Nonetheless, the independent predictive value of CAC for all-cause mortality is in line with earlier and recent angiography-based (37) and other CAC-based studies (18,38,39). Likewise, hsCRP contributed considerably to the assessment of all-cause mortality risk, which is in agreement with a recent multibiomarker study, where CRP was of little value for coronary risk prediction (40), while being an important predictor of all-cause mortality (40).

Taken together, elevated levels of CAC and hsCRP not only provide evidence of advanced coronary atherosclerosis and systemic inflammation, but in their presence, comorbidities seem to be associated with a greater risk of death. This is clinically relevant, as the risk from atherosclerosis burden can effectively be treated especially using statins (41). In addition, the Jupiter trial suggested that not only the coronary event risk, but also the risk of all-cause mortality may be reduced by targeting inflammation (14).

**Study limitations.** hsCRP is a nonspecific marker of inflammation. Other inflammatory markers such as Il-6 may provide valuable additional prognostic information.

In this study, data were acquired using EBCT scanners. MESA found equivalent reproducibilities for measuring CAC using EBCT and multidetector row helical computed tomography (MSCT) (42) and direct comparison studies also yielded comparable CAC quantities in EBCT versus MSCT (43), which suggests that our findings can be used clinically for data acquired on most MSCT scanners.

Our data suggest that extended risk assessment improves risk stratification and can guide decision making, especially in intermediate-risk individuals. Whether CAC- and hsCRP-driven risk-modifying therapy is justified by improved outcome must be tested in clinical trials. First-line recommendation in asymptomatic subjects remains a healthy lifestyle including smoking cessation, regular physical activity, weight control, and a healthy diet. The efforts that are necessary to implement effective lifestyle modification in larger cohorts must be weighed against the costs of extended risk assessment and the potential risk attributable to radiation exposure associated with CAC scoring.

## Conclusions

The risk of coronary events and all-cause mortality that is mediated by the presence of coronary atherosclerosis and systemic inflammation can be estimated by CAC and hsCRP. The improvement in risk prediction and discrimination was predominantly driven by CAC, whereas hsCRP appears to have a role especially in persons with low CAC scores.

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**Key Words:** all-cause mortality ■ coronary artery calcium (CAC) ■ coronary events ■ extended risk assessment ■ high-sensitivity C-reactive protein (hsCRP).

## APPENDIX

**For an expanded Acknowledgments section and a list of the members of the Advisory Board and the Criteria and Endpoint Committee, please see the online version of this article.**